2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO IODINE IN THE UNITED STATES

Iodine is an essential nutrient. Adequate intakes of iodine are required for the production of thyroid hormones. The term *iodine excess* is used in this profile to refer to increases in intake relative to estimated physiological requirements. As a reference point, the chronic dietary intake of iodine in U.S. populations has been estimated to range from approximately 150 to 950 µg/day. Estimates for various populations have ranged from <50 µg/day in iodine-deficient regions to >10 mg/day in populations that regularly ingest seaweeds containing a high iodine content. The National Research Council Recommended Dietary Allowance (RDA) for iodine is 150 µg/day (2.1 µg/kg/day for a 70-kg adult), with additional allowances of 25 and 50 µg/day during pregnancy and lactation, respectively.

The diet is the major source of iodine intake in the U.S. population. Iodine enters the human diet from a variety of natural sources, including mineral dissolution and atmospheric transport and deposition of seawater aerosols to surface water, vegetation, and soil. Major food categories that contribute to dietary iodine include marine produce (e.g., fish and shellfish) and milk. Cows and goats absorb iodine from ingested vegetation and water, when iodine is either deposited on the vegetation or in water or when the iodine is taken up by vegetation grown in soils containing iodine. The absorbed iodine is excreted into their milk; goat milk typically has higher concentrations of iodine than cow milk for equal deposition on feed. Additional sources of iodine in milk derive from the use of iodine disinfectants on cows, milking machines, and other milk processing equipment, as well as from supplementation of dairy feed with iodine-containing compounds. Breast milk is the primary source of iodine intake in nursing infants. Commercial infant formula preparations are fortified with sufficient iodine to support infant health, growth, and development. Cow milk is a significant source of iodine intake in children. Iodine is also intentionally added to the U.S. diet as iodized table salt and as iodine-containing bread dough oxidizers. Other sources of intake derive from the use of iodine-containing topical disinfectants (e.g., povidone-iodine), iodine-containing diagnostic and therapeutic agents, dietary supplements, and water purifiers containing iodine.

Thirty-five isotopes of iodine are recognized (^{108}I through ^{142}I). Only one isotope is stable (^{127}I); the remaining are radioactive. Most of these have radioactive half-lives of minutes or less. Twelve have half-lives that exceed 1 hour, and five have half-lives that exceed 1 day (^{124}I, ^{125}I, ^{126}I, ^{129}I, and ^{131}I). Three isotopes (^{125}I, ^{129}I, and ^{131}I) are of particular interest with respect to human exposures because ^{125}I and ^{131}I are used medically and all three are sufficiently long-lived to be transported to human receptors after their release into the environment. The U.S. population has been exposed to radioiodine in the general

environment as a result of atmospheric fallout of radioiodine released from uncontained and/or uncontrolled nuclear reactions. Historically, these have included surface or atmospheric detonation of nuclear bombs, routine and accidental releases from nuclear power plants and nuclear fuel reprocessing facilities, and from hospitals and medical research facilities. Estimates have been made of radiation doses to the U.S. population attributable to nuclear bomb tests conducted in the during the 1950s and 1960s at the Nevada Test Site; however, dose estimates for global fallout have not been completed. Geographic-specific geometric mean lifetime doses are estimated to have ranged from 0.19 to 43 cGy (rad) for people born on January 1, 1952 who consumed milk only from commercial retail sources, 0.7–55 cGy (rad) for people who consumed milk only from home-reared cows, and 6.4–330 cGy (rad) for people who consumed milk only from home-reared goats. Additional information is available on global doses from nuclear bomb tests, and doses from nuclear fuel processing, and medical uses can be found in UNSCEAR.

Individuals in the United States can also be exposed to radioiodine, primarily ^{123}I and ^{131}I, as a result of clinical procedures in which radioiodine compounds are administered to detect abnormalities of the thyroid gland or to destroy the thyroid gland to treat thyrotoxicosis or thyroid gland tumors. Diagnostic uses of radioiodine typically result in exposures by the oral or intravenous routes to 0.1–0.4 mCi (4–15 MBq) of ^{123}I or 0.005–0.01 mCi (0.2–0.4 MBq) of ^{131}I. These exposures correspond to approximate thyroid radiation doses of 1–5 rad (cGy) and 6–13 rad (cGy) for ^{123}I and ^{131}I, respectively. Cytotoxic doses of ^{131}I are delivered for ablative treatment of hyperthyroidism or thyrotoxicosis, exposures typically range from 5 to 15 mCi (185–555 MBq), which correspond to thyroid radiation doses of 5,000–10,000 rad (50–100 Gy). Higher exposures are used in the ablative treatment of thyroid gland cancer; 25–250 mCi (925–9,250 MBq), which correspond to thyroid radiation doses of 10,000–30,000 rad (100–300 Gy).

2.2 SUMMARY OF HEALTH EFFECTS

An extensive amount of literature is available on the effects of iodine on human physiology and health. The intense interest in iodine derives from early recognition of the necessity of appropriate amounts of iodine for maintenance of normal function of the thyroid gland and of awareness of diseases of the thyroid gland that are caused or affected by iodine intake. The prevalence of thyrotoxicosis (the clinical outcome of uncontrolled hyperthyroidism) has been estimated to be approximately 0.5%, and that of hypothyroidism is of a similar magnitude. Research directed at understanding the epidemiology, pathophysiology, and therapeutic strategies for these relatively common diseases have given way to a fairly comprehensive, although not complete, understanding of the role of iodine in thyroid gland physiology and the related health consequences and risks associated with excessive or inadequate iodine intake. The development of radiologic strategies for treating thyrotoxicosis, as well as studies of the

thyroid gland as a target for internal exposures to atmospheric radioactive fallout, have further complemented our understanding of iodine toxicity as it relates to exposures to radioactive isotopes of iodine.

This profile does not attempt to summarize in detail all of the studies relevant to iodine toxicity, as to do so would require several volumes. Instead, the focus is on literature that identifies the lowest observable exposure levels associated with iodine toxicity in humans. Where applicable, relevant studies in animals are summarized, particularly when such studies have identified potential targets of toxicity not already documented in humans or for which adequate dose-response information does not exist for humans. This strategy leads to a focus on the thyroid gland as the primary and most sensitive target of iodine for both chemical and radiologic toxicity. This is not surprising given that avid uptake of absorbed iodine by the thyroid gland results in approximately 90% of the body iodine content residing in the thyroid gland (see Section 3.3, Toxicokinetics). Adverse effects on a wide variety of other organ systems can result from disorders of the thyroid gland, including disturbances of the skin, cardiovascular system, pulmonary system, kidneys, gastrointestinal tract, liver, blood, neuromuscular system, central nervous system, skeleton, male and female reproductive systems, and numerous endocrine organs, including the pituitary and adrenal glands. Although these secondary effects are noted in the profile, they are not discussed in detail and the reader is referred to authoritative references on these subjects for further information.

An important consideration in interpreting the iodine toxicology literature is that the effect of an increase in iodine intake will depend, in part, on the preexisting background dietary intake and the associated physiological adaptations to background intake. The response to an upward excursion in intake may be quite different in individuals who have adapted to either low dietary or high dietary intake. Examples of this are described in appropriate sections of this report (e.g., Section 3.2.2.2). In this profile, the term molecular iodine is used to refer to I_2; the term *iodide* is used to refer to the anion, I^-, the term iodate is used to refer to the anion IO_3^-, and the term *iodine* is used to refer to the element in any form, usually when the form was not specified in the literature being summarized, or where the form is not relevant to the discussion. From a physiological perspective, regardless of the form of iodine that is absorbed after an exposure, iodide is the form of iodine that is taken up into the thyroid gland, and effects from exposures to iodine ultimately derive from exposure of the gland to iodide. A more important toxicological distinction is that, unlike iodide, molecular iodine (I_2) is a relatively strong oxidizing agent and has the potential to produce injuries related to redox reactions with proteins. This is the primary basis for the use of I_2 as a topical antiseptic and antimicrobial disinfectant for drinking water.

The health effects of exposure to radioiodine derive from the emission of beta and gamma radiation. Radioiodine that is absorbed into the body quickly distributes to the thyroid gland and, as a result, the tissues that receive the highest radiation doses are the thyroid gland and surrounding tissues (e.g.,

parathyroid gland). Tissues other than the thyroid gland can accumulate radioiodine, including salivary glands, gastric mucosa, choroid plexus, mammary glands, placenta, and sweat gland. Although these tissues may also receive a radiation dose from internal radioiodine, the thyroid gland receives a higher radiation dose. The radiation dose to the thyroid gland from absorbed radioiodine varies with isotope and its radiation emission properties (e.g., type of radiation, energy of emission, effective radioactive half-life). A comparison of the doses delivered to the thyroid gland from a few of the isotopes of iodine are compared in Table 2-1. The highest total doses are achieved with ^{131}I, whereas the highest dose rates (rad/hour) are delivered from ^{132}I.

Endocrine Effects. The principle direct effects of excessive iodine ingestion on the endocrine system are on the thyroid gland and regulation of thyroid hormone production and secretion. Adverse effects on the pituitary and adrenal glands derive secondarily from disorders of the thyroid gland. Effects of iodine on the thyroid gland can be classified into three types: hypothyroidism, hyperthyroidism, and thyroiditis. Hypothyroidism refers to the diminished production of thyroid hormone leading to clinical manifestations of thyroid insufficiency. This can occur with or without goiter, a functional hypertrophy of the gland that occurs in response to thyroid stimulating hormone (TSH) and suppressed thyroid hormone production. Typical biomarkers of hypothyroidism are a depression in the circulating levels of thyroxine (T_4) and/or triiodothyronine (T_3) below their normal ranges. This is usually, but not always, accompanied by an elevation of TSH (also known as thyrotropin) above the normal range. Hyperthyroidism is an excessive production and/or secretion of thyroid hormones. The clinical manifestation of abnormally elevated circulating levels of T_4 and/or T_3 is thyrotoxicosis. Thyroiditis refers to an inflammation of the gland, which is often secondary to thyroid gland autoimmunity. The above three types of effects of iodine can occur in children and adults, in fetuses exposed *in utero*, or in infants exposed during lactation. The primary effect of iodide excess in the fetus is goiter formation secondary to a suppression of thyroid hormone production and an elevation in TSH levels.

Measurements of serum levels of thyroid hormones and TSH are often used as biomarkers of hypothyroidism and hyperthyroidism in toxicology and epidemiology studies. In interpreting this literature in terms of human health risks, a distinction must be made between outcomes that have a high potential for producing clinical manifestations and those outcomes that are not clinically significant. In this profile, an observed decrease in circulating T_4 or T_3 levels or an increase in serum TSH level, within their respective normal ranges is referred to as *subclinical hypothyroidism.* Similarly, the term *subclinical hyperthyroidism* refers to a condition in which the circulating levels of T_4 or T_3 are elevated within their normal ranges. Typical normal ranges for these hormone levels are discussed in Section 3.8.2

An acute iodide excess can cause a decrease in thyroid hormone production in the thyroid gland; this effect is referred to as the *Wolff-Chaikoff effect*. In most people, this is followed by a return to normal

Table 2-1. Thyroid Doses and Dose Rates for Various Isotopes of Iodine[a]

Isotope	Percent of dose from beta radiation	Effective half-life in the thyroid (hours)	Mean range of beta-radiation in thyroid (mm)	Total dose from 1 mCi in the thyroid (rad)	Average dose rate of 10 rad from 1 mCi in the thyroid (rad/hour)
^{123}I	77	13	0.1	76	3.7
^{125}I	73	866	0.01	3,747	3.0
^{131}I	94	177	0.4	5,627	22
^{132}I	90	2.3	1.7	199	59
^{133}I	96	20	1.3	1,355	46
^{135}I	90	6.7	1.1	434	45

[a] from Maxon and Saenger 2000

levels of production, referred to as *escape* from the Wolff-Chaikoff effect, without clinically significant a change in circulating hormone levels. Escape is thought to be the result of down regulation of the iodine transport mechanism in the thyroid gland (see Section 3.4.3.2 for further details on the Wolff-Chaikoff effect). An acute or chronic excess of iodide can also decrease circulating T_4 and T_3 levels and induce a hypothyroid state. These effects are thought to involve the inhibition of the release of T_4 from the thyroid gland and/or inhibition of extrathyroidal production of T_3. Most iodine-induced hypothyroidism is transient, although T_4 replacement may be required in some patients. Hypothyroidism is thought to occur primarily in *susceptible* individuals who fail to escape from the inhibitory effect of large doses of iodide that produce the *Wolff-Chaikoff effect*. Susceptible individuals includes fetuses and newborn infants, patients who have autoimmune thyroiditis, patients with Graves' disease previously treated with iodine or antithyroid drugs, women who have had postpartum thyroiditis, or those who have had subacute thyroiditis. Spontaneous recovery usually occurs within 2–3 weeks, although some individual may develop permanent thyroiditis.

Several studies have examined the acute and intermediate-duration effects of increased intake of iodine on thyroid hormone status of adults. Acute iodine exposures (1,500 µg/day) have been shown to produce reversible thyroid gland hypertrophy, in addition to suppression of hormone production. The results of epidemiological studies suggest that chronic exposure to excess iodine can result in or contribute to hypothyroidism, with or without goiter, in children (1,150 µg/day, 29 µg/kg/day) and elderly adults (160–800 µg/day, 4–12 µg/kg/day). Several studies have found an increased prevalence of hypothyroidism in residents of areas of Japan where dietary iodine intake is extraordinarily high as a result of consumption of seaweeds with a high iodine content (13 mg/day, 0.22 mg/kg/day). Populations that are iodine deficient and, in particular, those that include people who have goiter, appear to be particularly sensitive to an increase in their iodine intake. For example, iodine supplementation (200–400 µg/day, 3–6 µg/kg/day) for treatment of endemic goiter has been associated with thyroid dysfunction, including thyroid autoimmunity.

People who have autoimmune thyroid disease may be at increased risk of developing thyroid dysfunction when exposed to excess iodide. Euthyroid patients who were diagnosed with Hashimoto's thyroiditis and who were positive for antithyroid (thyroid peroxidase) antibodies developed subclinical hypothyroidism after oral doses of 375 µg/day (4.5 µg/kg/day) for 6 months or clinical hypothyroidism after exposures to 180 mg I/day (2.6 mg/kg/day) for 6 weeks, more than 1,000 times the RDA. In general, iodine excess accelerates autoimmune thyroiditis in autoimmune-prone individuals, whereas iodine deficiency attenuates thryoiditis.

The clinical case literature demonstrates that doses of iodide exceeding 200 mg/day (2.8 mg/kg/day) given to a mother during pregnancy can result in congenital goiter and hypothyroidism in the newborn

infant. An iodine-deficient status of the mother can lead to goiter in the fetus and neurodevelopmental impairment of the fetus. Adequate iodine supplementation early in pregnancy can correct the deficiency and prevent maternal and neonatal goiter formation. Thyroid dysfunction was not detected in newborns of mothers who received oral doses of 3–4 µg/kg/day during pregnancy for the purpose of correcting or preventing potential iodine deficiency and for the management of Graves' disease during pregnancy (Graves' disease is a hyperthyroid state in which autoantibodies to the TSH receptor are produced and act on the TSH receptor to stimulate the gland to produce thyroid hormones).

Oral exposure to excess iodide can, under certain circumstances, induce hyperthyroidism and thyrotoxicosis. The epidemiological and clinical literature suggest that hyperthyroidism occurs most often in people who have a previous history of iodine deficiency, goiter, or thyroid diseases such as postpartum thyroiditis or Graves' disease. What has been referred to as an *epidemic* of hyperthyroidism occurred in the midwestern United States between the years 1926 and 1928. Clinical records suggest that the incidence of mortality from hyperthyroidism increased substantially during this period; for example, in Detroit, mortality from hyperthyroidism increased from approximately 2–4 deaths per 100,000 to approximately 11 deaths per 100,000. Although there is considerable debate about the origins of the epidemic, the advent of aggressive supplementation of the diet with iodide in midwestern endemic goiter areas has been implicated as a contributing factor. More recent and more rigorous epidemiologic designs have been applied to several populations in which dietary iodide was supplemented as a prophylaxis for iodine deficiency and goiter. These studies confirm that iodide supplementation of iodide-deficient diets, to achieve intakes in the range of 3–7 µg/kg/day, does indeed result in a detectable increase in incidence of hyperthyroidism. Cases of iodine-induced hyperthyroidism in people who were euthyroid and without apparent thyroid disease have also been reported; however, only a few have provided dose information, suggesting effects after oral doses of 3–1,440 mg/day (0.05–23 mg/kg/day) for 6 months.

Extensive clinical use of radioiodine, principally ^{123}I, ^{124}I, ^{125}I, and ^{131}I, for diagnostic purposes and for treatment of thyrotoxicosis has provided a wealth of information on the effects of relatively high acute exposures on thyroid gland function. Radioiodine is cytotoxic to the thyroid gland at high radiation doses and produces hypothyroidism when doses to the thyroid gland exceed 25 Gy (2,500 rad). Thyroid gland doses of approximately 300 Gy (30,000 rad) can completely ablate the thyroid gland and result in hypothyroidism. This dose is achieved with an acute exposure of approximately 25–250 mCi (0.9–9 GBq). Such high dosages are used to ablate thyroid remnants after surgery for thyroid cancer. Cytotoxic doses of ^{131}I can also produce dysfunction of the parathyroid gland, which can receive a radiation dose from β emission of ^{131}I in the adjacent thyroid gland.

Clinical cases have been reported in which congenital hypothyroidism occurred in newborn infants after maternal exposures to high doses of ^{131}I for treatment of thyroid gland tumors. However, the complex

clinical picture and pharmacotherapy of the mothers for their thyroid condition during pregnancy makes direct associations between the radioiodine exposure and clinical outcomes of the newborn unclear. Exposure in these case ranged from 11 to 77 mCi (407–2,850 MBq). Two studies that reviewed the thyroid status of larger sets of infants (37 or 73) born to patients who received ^{131}I for ablative treatment of thyroid cancer 2–10 years (mean, 5.3 years) prior to pregnancy (i.e., exposure occurred before conception and fetal development) found no thyroid gland disorders. The maternal ^{131}I exposures ranged from 1 to 17 GBq (50–400 mCi); the mean exposure was 3.5–4.4 GBq (100–120 mCi).

A large amount of epidemiological literature exists on the health outcomes in populations who were exposed to environmental releases of radioiodine. These include (1) releases from explosions of nuclear bombs such as the Marshall Islands BRAVO test, the largest U.S. detonation (15 megaton), and from the Nevada Test Site; (2) accidental releases from nuclear power plants such as the Chernobyl explosion and fire; and (3) releases from nuclear fuel production facilities such as the Hanford Nuclear Site (Table 2-2). In general, releases of these types result in mixed exposures to a variety of radioisotopes and to radiation doses from both external and internal exposure. However, doses from radioiodine that are significant to health derive largely from internal exposure as a result of uptake of radioiodine into the thyroid gland (see Section 3.4.2.2). The relative contribution of the inhalation and oral pathways can be expected to vary depending on the duration of the release and the duration of human access and contact to the sites of contamination. In the so-called *BRAVO cohort*, which has been studied extensively (see Section 3.3.1 for a more detailed discussion), inhalation may have been a more significant contributor to the internal radioiodine dose because the subjects comprising the cohort were evacuated from the site of major contamination within 2 days after the release of radioiodine to the atmosphere; this would have limited their dietary exposures. Nevertheless, estimates of inhalation intakes of airborne radioactivity amounted to <1% of the total intake estimated based on measurements of ^{131}I in urine, suggesting a substantial contribution from other routes. In nursing infants, exposure would have continued from ingestion of contaminated breast milk. The Chernobyl cohorts had access to contaminated areas and contaminated foods (e.g., locally harvested produce and goat and cow milk) for weeks to months after the accident. The thyroid radiation doses in this population are thought to have been dominated by the oral exposure pathway. Epidemiological studies of the Nevada Test Site detonations and releases from the Hanford Nuclear Site have focused on subjects who were potentially exposed through the dietary pathway as a result of repeated releases during periods of 7 or 13 years, respectively.

Radiation doses to the thyroid gland (external and internal) in the most highly exposed individuals after the Marshall Islands BRAVO test is estimated to have ranged from 0.3 to 20 Gy (30–2,000 rad). External radiation is estimated to have contributed approximately 4–16% or 10–50% of total thyroid dose, depending on the location of the individual with respect to the blast. Thyroid gland outcomes have been assessed periodically since the BRAVO test in 1954. Cases of thyroid gland disorders began to be

Table 2-2. Releases from Radioiodine-producing Events

Source	^{131}I Released (PBq)[a]	Reference
All nuclear bomb tests	650,000	Gonzalez 1998
Nevada Test Site nuclear bomb tests	5,500	NCI 1997
Chernobyl power plant accident	3,200	UNSCEAR 2000
Hanford Nuclear Site nuclear fuel processing-related releases	27	CDC 1999
Three Mile Island power plant accident	0.0004–0.0011	NRC 1995

[a]1 PBq=27,000 Ci

detected in the exposed population in 1964, 10 years after the BRAVO test, particularly in exposed children; these included cases of apparent growth retardation, myxedema (typical of hypothyroidism), and thyroid gland neoplasms. Collectively, the various health assessments and studies of the so-called *BRAVO cohort* have revealed dose-related abnormally high elevations in serum concentrations of TSH, characteristic of hypothyroidism. Among exposed children who were 1-year-old at the time of the BRAVO test and who received an estimated thyroid radiation dose exceeding 1,500 rad (or 15 Gy), 83% had serum concentrations of TSH >5 mU/L; thyroid nodularity was found in 67–81% of the most highly exposed group, and thyroid cancer was discovered in 6% of the most an apparent highly exposed group.

The 1986 explosion and fire at the nuclear power plant at Chernobyl in the Ukraine resulted in the release of airborne radionuclides to the surrounding regions and contamination of soil, food, and surface water. Several different exposure populations have been characterized that vary considerably in exposure levels and radiation doses received. These include emergency response workers who received the highest acute radiation doses, early evacuees from areas near the reactor (generally within 30 km of the reactor), and people who continued to inhabit contaminated areas outside the evacuation zone. The radiation exposures to the general population (i.e., evacuees and people who continued to inhabit contaminated areas) were attributed largely to isotopes of cesium (e.g., ^{137}Cs), which accounted for approximately 90–98% of the external radiation dose. However, radioiodine is estimated to have contributed approximately 50% of the total lifetime committed effective radiation dose for children born in the region in 1986, and approximately 80% of the radiation dose received during the first year after the release. Estimates of thyroid radiation doses to the general population suggest that doses were highest in children who were younger than 1 year of age at the time of the release. The highest estimated doses were received within the 30-km evacuation zone; median doses ranged from 2.3 Gy (250 rad) at age <1 year to 0.4 Gy (40 rad) in adolescents and adults. Estimated median doses received in populations residing 100–200 km from the plant (e.g., Mogilev region) were <0.3 Gy (30 rad) for all age groups. Thyroid screening programs and epidemiological studies conducted after the Chernobyl accident have revealed a dose-related elevated prevalence of thyroid nodules and thyroid cancer in children of the Belarus and Ukraine regions, apparent approximately 4 years after the Chernobyl accident. These effects have been associated with thyroid radiation doses of 0.3–1 Gy (30–100 rad). In both Belarus and the Ukraine, the highest rates of childhood thyroid cancer have occurred in areas where exposure to other industrial contaminants are likely to have occurred and where there is evidence for widespread iodine deficiency. These factors may have affected the early appearance of thyroid cancer after the accident, when vigorous public health screening programs for thyroid abnormalities were initiated. The incidence of thyroid cancer prior to the accident in these areas was poorly documented.

Immunological and Lymphoreticular Effects. Excess iodide intake may be a contributing factor in the development of autoimmune thyroiditis in susceptible individuals, which can result in hypothyroidism or hyperthyroidism (associated with Graves' disease). Autoimmune thyroiditis is an inflammation of the thyroid gland that can lead to fibrosis of the gland, follicular degeneration, follicular hyperplasia, and hypothyroidism. IgG autoantibodies to thyroglobulin and thyroid peroxidase are a consistent feature of the disorder. Iodine appears to play an important role in autoimmune response, as human lymphocytes recognize and proliferate in response to iodinated human thyroglobulin, but not iodine-free thyroglobulin. In general, iodine excess accelerates autoimmune thyroiditis in autoimmune-prone individuals, whereas iodine deficiency attenuates thryoiditis. Several studies have been conducted of people who reside in endemic goiter areas and who received iodide supplementation. These studies suggest that iodine intakes of 230–420 µg I/day (3.3–6.0 µg/kg/day total intake) for 12 months can induce thyroid autoimmunity. However, other studies have not found increases in autoimmunity associated with iodine supplementation at doses of 1,150 µg/day (29 µg/kg/day). Studies using rats have shown that doses of 70–95 mg I/kg/day (in drinking water) for 8–12 weeks may increase the incidence of autoimmune thyroiditis in inbred strains of rats that develop spontaneous thyroid autoimmunity.

Larger scale assessments of thyroid autoimmunity have been conducted in the Marshall Islands, where exposures to ^{131}I occurred as a result of fallout and contamination from test detonations of thermonuclear devises during the period 1946–1958. These studies have not revealed an elevated prevalence of thyroid autoimmunity relative to other populations. Studies of populations in the Belarus and Ukraine suggest a possible contribution of radioiodine exposure to an increased prevalence of thyroid autoimmunity following the Chernobyl accident. Cases of autoimmune hyperthyroidism, with serum antibodies to the TSH receptor, have occurred after exposures to higher levels of ^{131}I for ablative treatment of hyperthyroidism. No relationship was found between the prevalence or incidence of autoimmune thyroiditis and exposure to radioiodine associated with bomb tests at the Nevada Test Site.

Oral exposure to excess iodide can produce allergic reactions in sensitive subjects. The reactions include urticaria (hives), acneiform skin lesions (ioderma), and fevers. Cases of more serious reactions involve angioedema (localized edema), vasculitis, peritonitis and pneumonitis, and complement activation. Both humoral and cell-mediated immune responses are thought to be involved. In general, reactions to iodide have occurred in association with repeated oral doses of iodide 300–1,600 mg I/day (5–23 mg/kg/day). However, in many of these cases, preexisting disease and related drug therapy may have contributed to the reaction to the iodine; thus, the dose-response relationship for ioderma in healthy people remains highly uncertain.

Gastrointestinal Effects. Ablative treatment of thyroid cancers with ^{131}I has been associated with inflamation of the salivary glands (sialadentitis) in humans. Salivary glands express a transport protein, the sodium-iodine symport (NIS), which is also present in the thyroid gland, where it functions to transport iodide into the gland for hormone synthesis. Salivary glands can accumulate iodide in saliva at concentrations considerably above that in serum (see Sections 3.4.2.2 and 3.5.1). Exposures in reported cases of ^{131}I-induced sialadentitis ranged from 100 to 300 mCi (3.7–11 GBq). Sialadentitis usually occurred within a few days or weeks of exposure and had a duration of several weeks to 2–3 years.

Neurological Effects. Exposure to excess iodine has been shown to produce subclinical hypothyroidism, which in certain individuals sensitive individuals, may take the form of hypothyroidism. Sensitive populations include fetuses, newborn infants, and individuals who have thyroiditis or Graves' disease, many of whom have abnormal autoimmune disorders (see Section 3.2.2.2, Endocrine Effects). Of these iodine-induced forms of hypothyroidism, that occurring in the fetus or newborn infant has the greatest potential for producing neurological effects. This is because thyroid hormones are essential to the development of the neuromuscular system and brain. An iodine-induced hypothyroid state can result in delayed or deficient brain and neuromuscular development of the newborn. Iodine-induced hypothyroidism in an older child or adult would be expected to have little or no deleterious effects on the neuromuscular system. Exposure of a fetus to large amounts of radioiodine would result in thyroid tissue ablation and in similar delayed brain and neuromuscular development, if the hypothyroid state was not corrected (e.g., with hormone replacement therapy) after birth.

Exposure to excess iodine can also produce hyperthyroidism in sensitive individuals (see Section 3.2.2.2, Endocrine Effects). These include people who are initially iodine deficient, those who have thyroid disease, including Graves' disease, who have been treated with antithyroid drugs, people who have has postpartum thyroiditis, and those who have developed thyrotoxicosis from amiodarone or inteferon-alpha treatments. Patients who develop thyrotoxicosis may experience neuromuscular disorders, including myopathy, periodic paralysis, myasthenia gravis, peripheral neuropathy, tremor, and chorea.

Developmental Effects. Although iodine excess may result in hypothyroidism, iodine deficiency is far more likely to cause prenatal and postnatal hypothyroidism and be associated with neurologic injury leading to cretinism, a developmental effect (see Section 3.2.2.2, Endocrine Effects). Thyroid hormone deficiency from any cause at critical times of development may result in severe mental retardation, neurologic abnormalities, growth retardation, or abnormal pubertal development.

Congenital hypothyroidism secondary to thyroid ablation has been reported subsequent to maternal exposure to ablative doses of ^{131}I. In one case, an infant became hypothyroid after his mother received 99 mCi (3.7 GBq) of ^{131}I during her sixth week of pregnancy. Growth retardation was also observed in

some children who were exposed to radioiodine in the Marshall Island BRAVO cohort, early after the bomb test. Studies are suggestive of possible extra-thyroidal developmental effects of radioiodine following maternal exposures to ablative doses of ^{131}I received 2–10 years prior to pregnancy. Observed outcomes that may or may not have been related to the ^{131}I exposures included low birth weights with subsequent normal growth patterns, tetrology of Fallot (pulmonic stenosis, atrial septal defect, and right ventricular hypertrophy), hypoparathyroidism, Down's syndrome, and cardiac anomalies. The maternal ^{131}I exposures ranged from 1 to 17 GBq (20–460 mCi). Studies of pregnancy outcomes in Belarus and Ukraine populations after the Chernobyl accident are suggestive of possible developmental effects related to radiation exposures.

Exposure to excess iodine can also produce hyperthyroidism in sensitive individuals (see Section 3.2.2.2, Endocrine Effects). Growth acceleration occurs in childhood hyperthyroidism, from any cause, which is thought to be related to changes in pituitary regulation of growth.

Reproductive Effects. Exposure to excess iodine may produce hypothyroidism or hyperthyroidism (see Section 3.2.2.2, Endocrine Effects) and could cause disruption of reproductive function, secondary to thyroid gland dysfunction. Hypothyroidism can produce changes in the menstrual cycle in humans, including menorrhagia (excessive uterine bleeding) and anovulation (no ovulation). Spontaneous abortions, stillbirths, and premature births have also been associated with hypothyroidism. Reproductive impairments associated with hyperthyroidism include amenorrhea and alterations in gonadotropin release and sex hormone-binding globulin (SHBG), and associated changes in the levels and metabolism of steroid hormones in both females and males.

Clinical follow-up studies of pregnancies in patients who received ^{131}I (1–17 GBq, 20–460 mCi) for ablative treatment of thyroid cancer 2–10 years (mean, 5.3 years) prior to pregnancy have not shown evidence of effects on reproductive success. However, clinical cases of impaired testicular function following exposures to ^{131}I for ablative treatment of thyroid cancer in men have been reported. Observed effects included low sperm counts, azospermia (absence of spermatozoa), and elevated serum concentrations of follicle stimulating hormone (FSH), which persisted for more than 2 years. Exposures to radioiodine ranged from 30 to 1,335 mCi (1.1–49.5 GBq). In Belarus and Ukraine populations after the Chernobyl accident, pregnant women who resided in heavily exposed areas (including exposures to other industrial contaminants) appeared to be at risk for development of toxemia, renal insufficiency, and anemia.

Cancer. The relationship between iodide intake and thyroid cancer has been examined in several large-scale epidemiology studies. The results of these studies suggest that increased iodide intake may be a risk factor for thyroid cancer in certain populations, particularly in populations in iodine-deficient, endemic goiter regions. Not all studies have found an increased risk of cancer; however, a recurrent observation is an apparent shift in the histopathology toward a higher prevalence of papillary cancer after increased iodine intake in otherwise iodine-deficient populations. Two studies found a significant excess of thyroid gland cancer in populations from endemic goiter regions whose diets were supplemented to achieve approximate iodine intakes of 3.5 µg/kg/day.

The thyroid gland receives the highest radiation dose of any organ or tissue following internal exposure to radioiodine (see Section 3.4.2.2, Toxicokinetics), and therefore, cancer of the thyroid gland is a major cancer concern associated with radioiodine exposures. Cancer morbidity and mortality among populations who received exposures to radioiodine have been examined in several large-scale epidemiology studies. In general, these studies fall into several categories that can be distinguished by the sources of exposure and estimated radiation doses to the thyroid gland and include (see Table 3-3): (1) high exposures and doses (10–20 mCi, 370–740 MBq; >10,000 rad, >100 Gy) achieved when ^{131}I is administered to treat hyperthyroidism (higher exposures are used in treatment of thyroid cancer); (2) lower exposures and doses (40–70 µCi, 1.5–2.6 MBq; 80–130 rad, cGy) associated with clinical administration of ^{131}I for diagnosis of thyroid gland disorders; (3) doses from exposures to fallout from nuclear bomb tests (BRAVO test, 300–2,000 rad, cGy; Nevada Test Site, 1–40 rad, cGy); (4) doses from exposures to releases from nuclear power plant accidents (Chernobyl, 1–200 rad, cGy), and (5) exposures from operational releases from nuclear fuel processing plants (Hanford Nuclear Site, 0.0001–284 rad, cGy).

The relatively high and acutely cytotoxic radiation doses to the thyroid gland that are achieved in the treatment of thyroid gland disorders, and the related outcomes on the thyroid, are virtually irrelevant to predicting outcomes from the much lower environmental exposures that occur in most U.S. populations. Nevertheless, these studies have revealed that, even at high exposures (3–27 mCi, 111–999 MBq) and thyroid gland doses (60 Gy, 6,000 rad), significant risks for cancers in organs other than the thyroid gland have not been consistently detected when the study designs control for other treatments administered to the patients. Studies of diagnostic doses of radioiodine have not consistently revealed significant risks of thyroid or other cancers; those that have, however, found significantly elevated risks only in patients who were administered the radioiodine for diagnosing a suspected thyroid gland tumor. In general, studies of the outcomes of medical uses of radioiodine involve subjects who were exposed as adults. Studies of thyroid cancers and external radiation exposure have found a strong age dependence between thyroid radiation dose and thyroid cancer. Risk is substantially greater for radiation doses received prior to age 15 years when compared to risks for doses received at older ages. This same general trend in age-

dependence would be expected for internal exposures to radioiodine, thus, studies of adult exposures to radioiodine may not be directly applicable to predicting outcomes from exposures to children. Studies of populations potentially exposed to radioiodine (0.09–3.2 Gy, 9–325 rad) as a result of nuclear bomb tests at the Nevada Test Site are suggestive, but not conclusive, of a possible association between radioiodine exposures and thyroid cancer. The National Research Council concluded that, because of uncertainties related to dose reconstruction and epidemiological analyses of the Nevada Test Site experience, the currently available information is not adequate to determine the extent to which the bomb tests in Nevada increased the incidence of thyroid cancer. A case-control study of thyroid cancers among children in Belarus provides reasonably strong evidence for the contribution of higher level radioiodine exposure and thyroid cancers diagnosed after the Chernobyl accident.

Breast cancer is also a concern with exposures to high levels of radioiodine after ablative therapy for hyperthyroidism because the breast expresses NIS and can transport and accumulate iodide (see Sections 3.4.4.2 and 3.5.1, Distribution). However, the epidemiological literature to date has not implicated such exposures as a significant risk factor for breast cancer.

2.3 MINIMAL RISK LEVELS

Inhalation MRLs

- An MRL could not be derived for iodine because of a lack of information on dose-response relationships for the inhalation pathway.

Oral MRLs

- An MRL of 0.01 mg/kg/day has been derived for acute-duration oral exposure (1–14 days) to iodine.

The acute-duration MRL is based on a no-observed-adverse-effect-level (NOAEL) of 0.024 mg/kg/day in healthy adult humans. Although the NOAEL is derived from acute studies of health adults, supporting studies indicate that the NOAEL would be applicable to children and elderly adults. On this basis, an uncertainty factor is not needed adjust the NOAEL to account for human variability in sensitivity.

Although elevated serum concentrations of TSH and decreased serum concentrations of thyroid hormone (T_4 and T_3) in healthy adults who had no history of thyroid disease or detectable antithyroid antibodies, hormone levels were within the normal range for healthy adults. Furthermore, the hormone levels reverted to pretreatment levels when the iodine dosage was withdrawn.

Healthy euthyroid adults (9 males, 9 females) who had no history of thyroid disease or detectable antithyroid antibodies received daily oral doses of 250, 500, or 1,500 µg I/day as sodium iodide for 14 days. Based on 24-hour urinary excretion of iodide prior to the iodide supplement, the background iodine intake was estimated to be approximately 200 µg/day; thus, the total iodide intake was approximately 450, 700, or 1,700 µg I/day (approximately 0.0064, 0.01, or 0.024 mg/kg/day, assuming a 70-kg body weight). Subjects who received 1,700 µg/day (0.024 mg/kg/day) had significantly depressed (5–10%) serum concentrations of TT_4, FT_4, and TT_3 compared to pretreatment levels, and serum TSH concentrations were significantly elevated (47%) compared to pretreatment values. Hormone levels were within the normal range during treatment. In this same study, nine females received daily doses of 250 or 500 µg I/day for 14 days (total intake was approximately 450 or 700 µg/day; 0.0064 or 0.010 mg/kg/day) and there were no significant changes in serum hormone concentrations.

In similar type of study, healthy, euthyroid, adult males (n=10) received daily oral doses of 500, 1,500, or 4,500 µg I/day (as sodium iodide) for 14 days. Based on 24-hour urinary excretion of iodide prior to the iodide supplement of 250–320 µg/day, the total estimated intakes were 300, 800, 1,800, or 4,800 µg/day or approximately 0.004, 0.011, 0.026, or 0.069 mg/kg/day. There were no effects on serum thyroid hormone or TSH concentrations at the 800 µg/day intake (0.011 mg/kg/day); however, intakes of 1,800 or 4,800 µg I/day (0.026 or 0.064 mg/kg/day) produced small (10%) but significant, transient decreases in serum TT_4 and FT_4 concentrations and an increase (48%) in serum TSH concentration, relative to the pretreatment values.

Although the acute NOAEL is derived from acute studies of health adults, supporting studies indicate that the NOAEL would be applicable to children and elderly adults. On this basis, an uncertainty factor is not needed adjust the NOAEL to account for human variability in sensitivity. In the Chow et al. study, 30 healthy elderly adult females, without evidence of thyroid peroxidase antibodies (TPA), received daily doses of 500 µg I/day (as potassium iodide) for 14 or 28 days. Serum concentrations of FT_4 were significantly decreased and serum TSH concentrations were significantly elevated in the women who received the iodide supplements, relative to a placebo control group. On average, the magnitude of the changes did not produce clinically significant depression in thyroid hormone levels; however, five subjects had serum TSH concentrations that exceeded 5 mU/L. The subjects had a lower dietary iodine intake than those in the Gardner et al. study, approximately 72–100 µg/day, based on urinary iodide measurements. Therefore, the total iodide intake was approximately 600 µg/day or 0.0086 mg/kg/day, essentially the same as the acute NOAEL in healthy adults based on Gardner et al. and Paul et al.

In the Boyages et al. study, thyroid status was compared in groups of children, ages 7–15 years, who resided in two areas of China where drinking water iodide concentrations were either 462 µg/L (n=120) or 54 µg/L (n=51). Although the subjects were all euthyroid with normal values for serum thyroid

hormones and TSH concentrations, TSH concentrations were significantly higher in the high iodine group. The prevalence and severity of goiter in the population were evaluated, the latter based on a goiter severity classification scale (Grade 0, no visible goiter; Grade 1, palpable goiter that is not visible when the neck is not extended; Grade 2, palpable and visible goiter when the neck is not extended). The high iodide group had a 65% prevalence of goiter and a 15% prevalence of Grade 2 goiter compared to 15% for goiter and 0% for Grade 2 goiter in the low iodine group. Urinary iodine was 1,236 µg I/g creatinine in the high iodine group and 428 µg I/g creatinine in the low iodine group. Assuming a body weight of 40 kg and lean body mass of 85% of body weight, the above urinary iodine/creatinine ratios are approximately equivalent to iodine excretion rates, or steady state ingestion rates of 1,150 (0.029 mg/kg/day) and 400 µg/day (0.01 mg/kg/day) in the high and low iodide groups, respectively. The NOAEL of 0.01 mg/kg/day from this study is the same as the acute NOAEL based on Gardner et al. and Paul et al.

The MRL is higher than the National Research Council RDA of 150 µg/day (0.0021 mg/kg/day for a 70-kg adult), with additional allowances of 25 µg/day (0.0025 mg/kg/day) and 50 µg/day (0.0029 mg/kg/day) during pregnancy and lactation, respectively.

- An MRL of 0.01 mg/kg/day has been derived for chronic-duration (>364 days) oral exposure to iodine.

The chronic-duration MRL is based on a NOAEL of 0.01 mg/kg/day and a lowest-observed-adverse-effect level (LOAEL) of 0.029 mg/kg/day for subclinical hypothyroidism in healthy human children. An uncertainty factor is not needed adjust the NOAEL to account for human variability in sensitivity because the NOAEL is based on a sensitive end point in children, a sensitive subpopulation. Supporting studies indicate that the NOAEL would be applicable to elderly adults who may represent another sensitive subpopulation. The chronic MRL was based on a chronic human study; however, since the chronic MRL is the same as the acute MRL (0.01 mg/kg/day), it is also applicable to intermediate-duration exposures.

Although serum concentrations of TSH were elevated, they remained within the normal range for children. Thyroid gland enlargement, however, was observed in children who had no history of thyroid disease or detectable antithyroid antibodies. Hormone levels were within the normal range for healthy children; therefore, these dosages did not induce clinical hypothyroidism. The slight thyroid enlargement can be considered a less-serious LOAEL, not indicative of functional impairment. Thyroid status was compared in groups of children, ages 7–15 years, who resided in two areas of China where drinking water iodide concentrations were either 462 µg/L (n=120) or 54 µg/L (n=51). Urinary iodine was 1,236 µg I/g creatinine in the high iodine group and 428 µg I/g creatinine in the low iodine group. Assuming a body weight of 40 kg and lean body mass of 85% of body weight, the above urinary iodine/creatinine ratios are approximately equivalent to iodine excretion rates, or steady state ingestion rates of

1,150 (0.029 mg/kg/day) and 400 µg/day (0.010 mg/kg/day) in the high and low iodide groups, respectively. Although the subjects were all euthyroid with normal values for serum thyroid hormones and TSH concentrations, TSH concentrations were significantly higher (33%) in the high iodine group. The high iodide group had a 65% prevalence of goiter and a 15% prevalence of Grade 2 goiter compared to 15% for goiter and 0% for Grade 2 goiter in the low iodine group.

Although the acute NOAEL is derived from acute studies of children, supporting studies indicate that the NOAEL would be applicable to elderly adults. On this basis, an uncertainty factor is not needed adjust the NOAEL to account for human variability in sensitivity. In the Chow et al. study, 30 healthy elderly adult females, without evidence of TPA, received daily doses of 500 µg I/day (as potassium iodide) for 14 or 28 days. Serum concentrations of FT_4 were significantly decreased and serum TSH concentrations were significantly elevated in the women who received the iodide supplements, relative to a placebo control group. On average, the magnitude of the changes did not produce clinically significant depression in thyroid hormone levels; however, five subjects had serum TSH concentrations that exceeded 5 mU/L. The pre-existing dietary iodine intake was approximately 72–100 µg/day, based on urinary iodide measurements. Therefore, the total iodide intake was approximately 600 µg/day or 0.0086 mg/kg/day, essentially the same as the acute NOAEL in healthy adults based on Boyages et al. and Li et al.

Szabolcs et al. studied elderly nursing home residents in the Carpathian Basin and revealed a prevalence of hypothyroidism that increased with increasing iodine intake. Subjects were from one of three regions where, based on reported urinary iodine levels of 72, 100, or 513 µg I/g creatinine, the iodine intakes were approximately 117, 163, or 834 µg/day (0.0017, 0.0023, or 0.012 mg/kg/day for low, n=119; moderate, n=135; or high intake, n=92, respectively). The prevalence of elevated serum TSH concentrations together with serum FT_4 concentrations below the normal range was 0.95, 1.5, and 7.6% in the low, moderate, and high iodine groups, respectively. If a prevalence of abnormal thyroid hormone levels of <5% is considered a NOAEL, than this study supports a NOAEL in elderly adults that is slightly below 0.012 mg/kg/day. Linear interpolation of the dose-prevalence data reported above yields an estimate of a 5% prevalence at an iodine intake of approximately 0.008 mg/kg/day.

The MRL is higher than the National Research Council RDA of iodine of 150 µg/day (0.0021 mg/kg/day for a 70-kg adult), with additional allowances of 25 µg/day (0.0025 mg/kg/day) and 50 µg/day (0.0029 mg/kg/day) during pregnancy and lactation, respectively.